Synthesis of Degradable Monomers for Ring-Opening Metathesis Polymerization

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Introduction

In the field of polymer chemistry, ring opening metathesis polymerization (ROMP) is one of the most versatile and effective methods of polymerization.[1] ROMP is a type of olefin metathesis chain-growth polymerization that is relatively easy to use, making it popular in the field of polymer chemistry. ROMP reactions are driven by relieving ring strain from cyclic olefins, such as norbornene and cyclobutene, although alkynes have also been used as directing group for ROMP.[2] One of the more commonly used catalyst for ROMP reactions is the third-generation Grubbs catalyst (known as G3).[3] The G3 catalyst shows fast initiation and propagation, air stability, and tolerates nearly all functional groups, making it possible to polymerize a wide variety of monomers.[4] Combining ROMP with the G3 catalyst has led to the development of a wide range of new polymers that were previously inaccessible. One category of polymers that has not been studied much using these techniques is degradable polymers, and the ones that have been developed are not that effective. One example is a monomer developed by Dr. Laura Kiessling et al. which undergoes ring-opening metathesis polymerization, but still requires harsh conditions to degrade.[5]

Developing degradable polymers is a potential solution to the large increase in concern about many commercially used polymers, as many of them degrade very slowly. An example is polystyrene, the main component of styrofoam products, which in addition to being slow to biodegrade is also resilient to decomposition by acids and bases.[6] As these products have accumulated, they have had an increasing impact on the environment and are now a major world concern. Being able to make more degradable polymers could be a potential solution to this. One method of creating degradable polymers is to integrate functional groups into the backbone of the polymer that degrade in mild conditions. The functional group that we aim to incorporate is an

acetal group. Polyacetals were first reported in 1912,[7] and since then many varieties of polyacetals and polycycloacetals have been synthesized and reported. Some methods of creating polyacetals include, but are not limited to, reacting dialdehydes and tetraols, reacting diketones and tetraols, polytransacetalization, and polyaddition of diols to divinyl ethers.[8] However, most of these reactions involve exchanges of acetals or hydroxyl groups on the end of the monomers. Not much research has been done on acetal-containing monomers prepared for metathesis polymerization, and the ones that have been reported make use of the Grubbs 1 catalyst.[9]

The objective of this research was to discover a synthetic route to develop a monomer **(4)**, that when polymerized using ROMP with a Grubbs 3 catalyst would create a polymer that could be degraded easily.

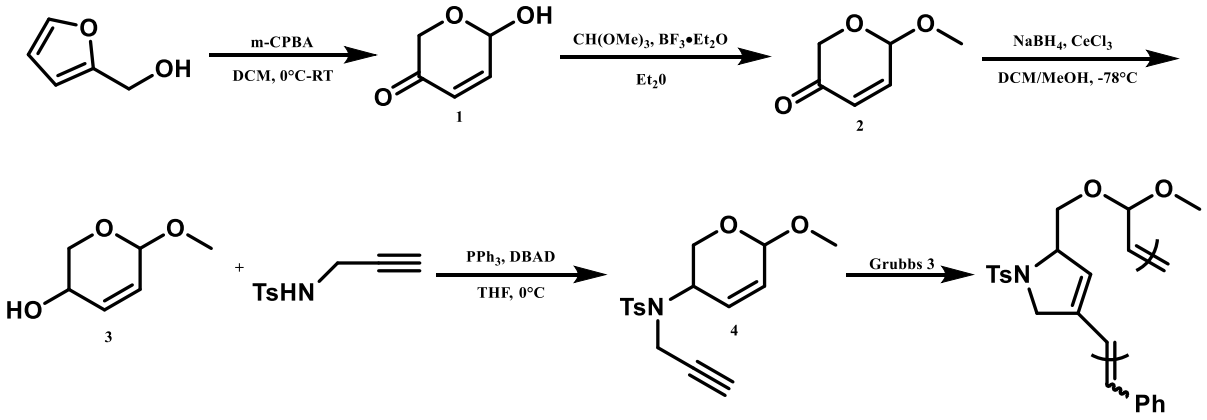

Figure 1. Proposed synthetic route of forming monomer **(4)**.

With this acetal in the backbone of the polymer, it should be degradable in mildly acetic conditions. In addition, since acetals degrade in biologically relevant pH ranges (< 7.4), there are potential applications in drug delivery systems of this monomer. The Grubbs 3 catalyst works with a variety of functional groups, the properties of the degradable monomer can be altered to fit a range of requirements. Most notably, the group attached to the acetal and the group attached to the nitrogen can be altered to affect polymerization. Polymerization should also be dependent on which

diastereomer, either *cis*- or *trans*-, of the monomer is being polymerized. Successful synthesis and polymerization of this monomer will lead to the development of a degradable polymer that can be used for a variety of applications both industrially and in the field of polymer chemistry.

Literature Review

As environmental concern continues to rise over many common commercial plastics and polymers, the need for more easily degraded monomers has become pertinent. While there are many different ways to form polymers, ring-opening metathesis polymerization (ROMP), a chain-growth polymerization of strained cyclic olefin-containing monomers, has shown great versatility in the field of polymer chemistry. The first patent on what would come to be known as ROMP was issued to DuPont in 1955.[10] The development of ill-defined ROMP catalyst systems continued in a number of research groups, notably at DuPont[11] and in Natta's group,[12] and Calderon and co-workers at Goodyear carried out fundamental work into understanding the metathesis mechanism and applications.[13] A large development in ROMP was made by Gilliom and Grubbs in the 1980s when they discovered conditions for carrying out the living ROMP of norbornene with titanacyclobutane initiators.[14] Subsequently, Schrock and co-workers reported a similar accomplishment with a tantalum catalyst,[15] as did Schrock, Grubbs, and co-workers with a tungsten catalyst.[16] Today, one of the more common type of ROMP catalysts are those containing ruthenium, the most notable being the Grubbs 3 catalyst.[17] Although our work makes use of the Grubbs 3 catalyst and ROMP, our goal is not to improve ROMP but to create degradable monomers that can make use of ROMP and the Grubbs 3 catalyst, with our focus being on polyacetals.

Polyacetals have a long history dating back to 1912 where they were first reported by John Read.[18] Recently, interest in polyacetals and polycycloacetals has been on the rise because of their various properties and that many of their building blocks come from renewable resources.[19] Polyacetals are typically soluble and degradable in biologically relevant pH ranges, and polycycloacetals have rigid backbones resulting in favorable thermal and mechanical properties.[20] There have been many synthetic pathways created to make polyacetals and polycycloacetals. Again, the first method of synthesizing them was created by John Read when he performed a condensation reaction between glyoxal and pentaerythritol,[21] which has been expanded to a more general reaction between dialdehydes and tetraols. More recently, Miller and co-workers investigated polycycloacetals from pentaerythritol and various dicarbonyl monomers, forming polymers with high molecular weight.[22] They also emphasized the fact that all dicarbonyl monomers were derived from natural products. Polyacetalization from diketone monomers is less frequently reported but has been observed, although the reaction of pentaerythritol with 1,4-cyclohexanedione to form a spiro polycycloacetal has piqued interest because of the renewable nature of 1,4-cyclohexanedione.[23] Other methods of forming polyacetals include using keto-carboxylic acids,[24] performing nucleophilic substitution and addition polymerization,[25] and cationic ring opening polymerizations.[26] A less common method of forming polyacetals is through ring-opening metathesis polymerization.

Although there has been research performed on synthesizing acetal-containing monomers for metathesis polymerizations, including ROMP, only a few monomers have actually been tested and the results are less than ideal.[27] ROMP has been used to synthesize copolymers of cyclooctadiene and 4,7-dihydro-1,3-dioxepins, where the latter were either formaldehyde or benzaldehyde acetals.[28] Unfortunately, the polymerizations resulted in low conversion, long

reaction times (15 hours), and high dispersity. When tested on how well the polymers degrade the benzaldehyde product hydrolyzed well, but the polymer based on formaldehyde required a harsher two-step process. A benzaldehyde acetal (bis(5-hexenoxy)methylbenzene) was also subjected to acyclic diene metathesis polymerization (ADMET), but like the ROMP reactions the reaction time was very long.[29] After 60 hours, high molecular weight polyacetals were obtained but the dispersity was still an issue.

Our research will aim at improving the functionality of using ring-opening metathesis polymerizations to make polyacetals by making monomers that are more effective in ROMP. The three main issues currently in making polyacetals through ROMP are long reaction times, low conversion, and large dispersity. By incorporating enynes to direct polymerization and other functional groups to alter the properties of the monomer, we hope to create monomers that react quickly, have full conversion, and low disparity. In addition, degradability testing will be performed to see if any of the degradable polymers have any potential application commercially, or elsewhere in the field.

Methodology

I. Designing Degradable Monomer

The goal of our project was to design degradable monomers that are compatible with ring-opening metathesis polymerization (ROMP). To accomplish this, we designed a monomer based on the work of Dr. Tae-Lim Choi, who synthesized a cyclic monomer containing and olefin and an alkyne directing group attached to the ring.[30] This monomer undergoes a very fast ring-opening/ring-closing polymerization when used with the Grubbs 3 catalyst, so it was an excellent

basis for our project. The modification we made to the monomer was to incorporate an acetal group into the ring structure. Acetals are easily broken apart in mildly acidic and biologically relevant pHs, which is the property we wanted for our monomer. This property carries over when incorporated into polymers, so modifying Choi's monomer in this way seemed like a good starting target for our project.

II. Synthesizing Base Monomer

The first and simplest monomer we wanted to synthesize had a methoxy group as part of the acetal and a tosyl group attached to the amine that connected to the alkyne. These were chosen because they are both fairly easy synthetically to incorporate into the monomer since there shouldn't be many steric issues since they are relatively small groups. The starting material for our synthetic scheme was furfuryl alcohol, a compound derived from corn which is both inexpensive, renewable, and easy to ring-open into the six-membered ring that Dr. Choi made, except that it would contain the hemiacetal that we would later modify. The ring-opening was performed using the Achmatowicz rearrangement. The remainder of the synthesis included a variety of common synthetic reactions, most notably the Mitsunobu and Tsuji-Trost reactions. For all new compounds synthesized, ^{1}H NMR, ^{13}C NMR, mass spectroscopy, and melting point data were gathered.

The monomer was then polymerized using the third-generation Grubbs catalyst, which was chosen for its fast initiation speed and high tolerance for varying functional groups. The resulting polymer was analyzed by gel permeation chromatography (GPC) in order to measure its molecular weight (M_n) and polydispersity index (PDI). We want the polymer to be easily degradable under mild conditions, but we also want it to be stable and usable too. To test its stability, we stored it in a fridge at 4°C for four weeks and regularly monitored it with GPC to see if there were any changes in M_n, which would indicate degradation.

III. Testing Stereochemical Effects on Polymerization

There are multiple aspects of our monomer that can be varied, one of which is its stereochemistry. It is possible for the monomer to exist in either a *cis* or *trans* configuration across the ring structure. Dr. Choi's group briefly commented on this in their paper, stating that the *trans*-monomer seemed to have a higher percent conversion and lower PDI when polymerized as compared to the *cis*- monomer. We wanted to confirm if this was observed with our monomer. The synthetic scheme for making the *cis* monomer is shown in **Figure 2**, and the scheme for making the *trans* monomer is shown in **Figure 3**. Once the monomers were made, they were polymerized and analyzed with GPC to determine which one performed better.

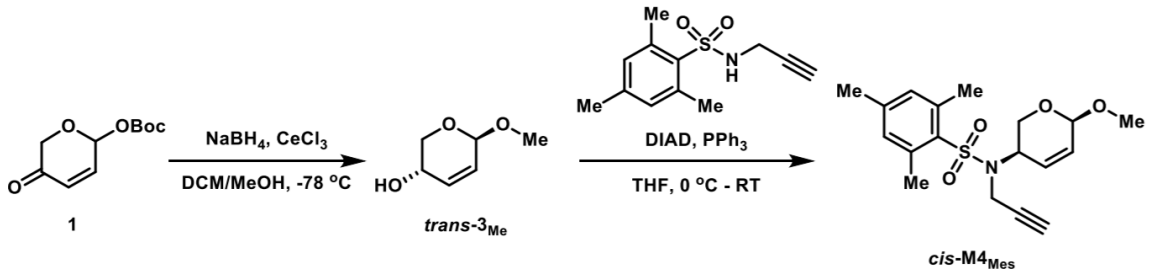

Figure 2. Synthetic scheme for making *cis*-$M4_{Mes}$ monomer starting from Boc protected group

IV. Testing Polymerization of Variations of Monomer

Once it was established which diastereomer polymerized better, we began testing variations of it. Both the acetal group and the sulfonamide could be exchanged in the reaction scheme to give varying monomers. The initial monomer had rather non-bulky groups attached to it, so we wanted to observe what effects changing the bulk and sterics of the monomer would have on polymerization. To do this, mesyl and trisyl groups were substituted for the tosyl group and benzoxy or other longer-chain hydrocarbons were used to replace the methoxy group. The reaction scheme remained basically the same for these substitutions, other than changing the reactants

based on what group we were attaching. The general scheme along with the different groups tested can be seen in **Figure 3**. Again, all products were analyzed using the previously mentioned characterization techniques. After polymerization, GPC analysis was performed on the polymers to see what effects changing the bulk of the monomer had on the molecular weight and PDI of the polymer.

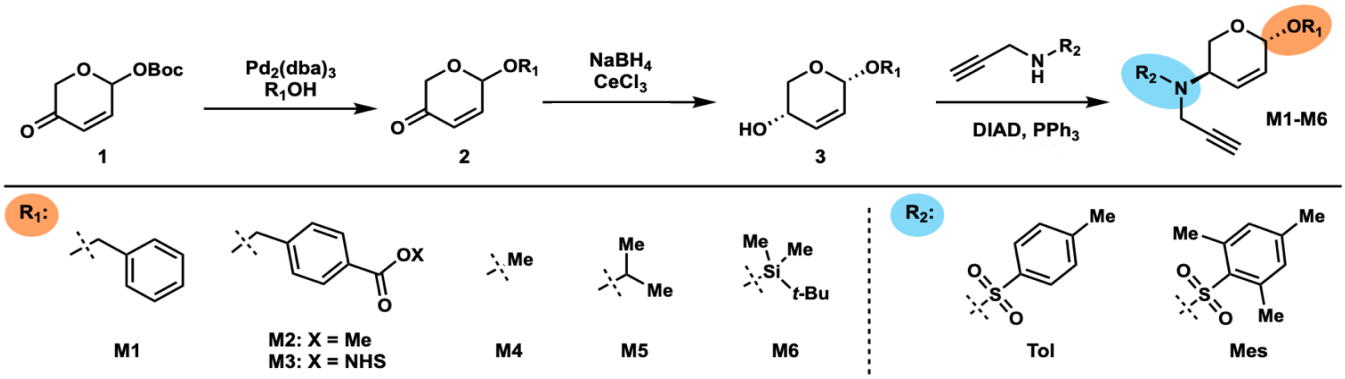

Figure 3. General synthesis of *trans* monomers starting from Boc protected group along with different acetal and sulfonamide groups.

V. Limitations

The main limitation of the project was the finite amount of variations of the monomer we were able to test. It is impossible to test every possible variation of the monomer, and although some may be very similar, polymerizations of the variations will be slightly different. Because our monomer can have both the acetal and sulfonamide varied, this greatly diversifies the potential monomers we could make. This is then compounded by the fact that for every monomer there exists two diastereomers, the *cis* and *trans*.

To minimize this issue, we systematically made alterations to the monomer and drew general conclusions from these. To test the effects of stereochemistry, we made the *cis* and *trans* versions of the same monomer and analyzed the polymers formed. To test the different acetal groups, we kept the sulfonamide group constant and varied the acetal. Then we did the opposite to

test the effects of the sulfonamide group. From these we were able to make generalizations about expected trends that arise from these changes to the monomer.

Results and Discussion

Using the reaction pathway proposed in **Figure 1**, we were successfully able to synthesize the monomer with the methoxy group attached to the acetal. Unfortunately, the overall yield of the monomer was low, although enough was obtained to test polymerization. The reactions and their respective yields are shown below in **Figure 4**.

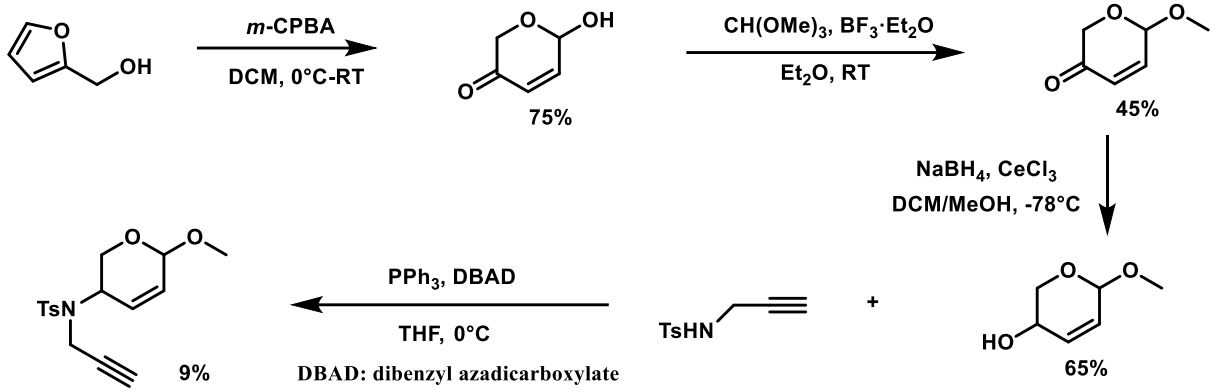

Figure 4. Reaction steps with percent yields.

Another issue noticed with this pathway is that it lacked stereochemical control, which later complicated polymerizations. To determine the difference between the diastereomers, the initial synthetic pathway was altered to be able to selectively produce the *cis* and *trans* monomers. Both new pathways started with the same Achmatowicz rearrangement of furfuryl alcohol, which then had the hydroxy group replaced with a Boc protecting group. The reaction pathways split from there, but both yielded their respective monomer with decent yields. The synthetic path to make the *trans* monomer is shown in **Figure 5** along with the respective yields.

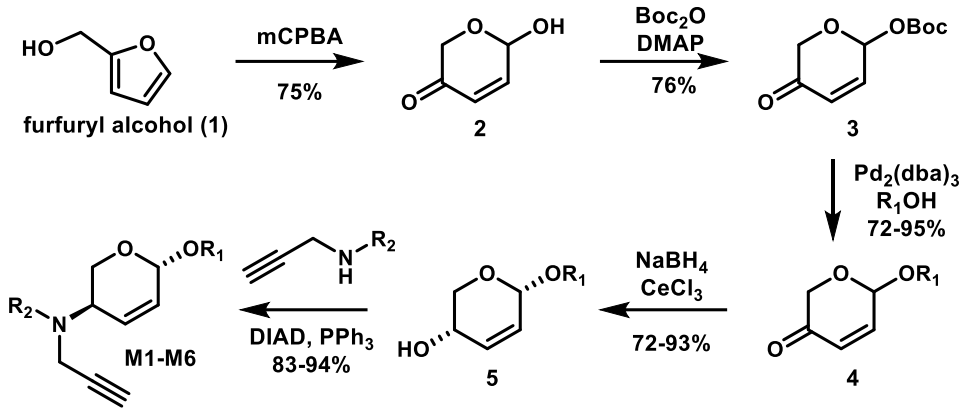

Figure 5. General synthesis of *trans* monomer with yields.

To test polymerization, the *cis* and *trans* methoxy variations of the monomer were both polymerized using the Grubbs 3rd generation catalyst. The *trans* version greatly outperformed the *cis* diastereomer, having a percent conversion of over 95% in only 10 minutes whereas the *cis* monomer only had 29% conversion after 20 minutes. If cyclization is the rate-limiting step, this difference can be explained by the conformational equilibrium of the half-chair monomer structure. In order to cyclize onto the six-membered ring after alkyne addition, the sulfonamide substituent needs to be in a pseudo-axial position. For the *trans* monomer, the acetal must also be in the pseudo-axial position, but this is assisted by the anomeric effect. But for the *cis* monomer, equilibrium favors the sulfonamide to be pseudo-equatorial, which would then require a unfavored ring-flip for cyclization.

Once it was established that the *trans* diastereomer of the monomer was the ideal version, different variations of the monomer were tested by varying the sulfonamide and acetal. Because of the synthetic path used, shown in **Figure 3**, it was very easy to make these substitutions. The Tsuji-Trost reaction served as our first point of diversification, as the Boc protecting group could readily be exchanged for a variety of alkyl acetal derivatives to give molecule **2**. On the final step,

a Mitsunobu inversion of the alcohol with either tolyl **(Tol)** or mesityl **(Mes)** propargyl sulfonamide could be performed, again altering the monomer.

Before testing the polymerizations of the different monomers, the **M1$_{Mes}$** monomer was polymerized at different degrees of polymerization (DP) in order to assess if it is possible to target specific molecular weights for the corresponding polymer. **Figure 6** shows the GPCs for **P1$_{Mes}$** at various DPs, as well as the molecular weights of the polymers at the different DPs.

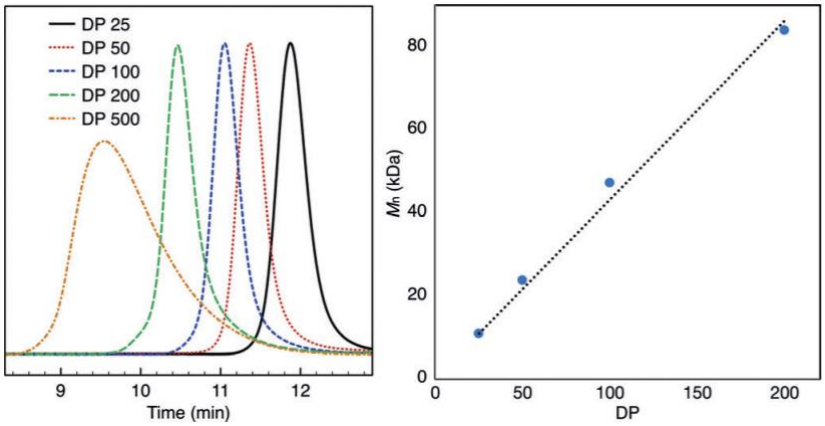

Figure 6. SEC chromatogram of **P1$_{Mes}$** at varying DPs (left) and linear correlation of M_n vs DP (right).

As seen in the graph of molecular weight vs DP, there is a fairly linear correlation between the two up until DP 200. Based on this plot, any molecular weight for this polymer within this range can be targeted by using the appropriate monomer to initiator ratio. But when the monomer was polymerized at DP 500, this trend fell apart. The PDI of the polymer greatly increases and a wide range of molecular weights is obtained at this monomer to initiator ratio. The tosyl variation of this monomer was also tested but demonstrated larger PDIs and less control over molecular weights. This is believed to be due to steric factors, in that the smaller tosyl group allows for more opportunities for cross-linking to occur compared to the mesyl version. As such, the mesyl variations of the monomers were the ones primarily synthesized because of their better performance.

As a last part of the experiment, we tested the polymerizations of many different monomers. The different monomers are shown in **Figure 7.** These monomers were polymerized in the same conditions and analyzed using GPC in order to measure the polymers' molecular weights and PDIs.

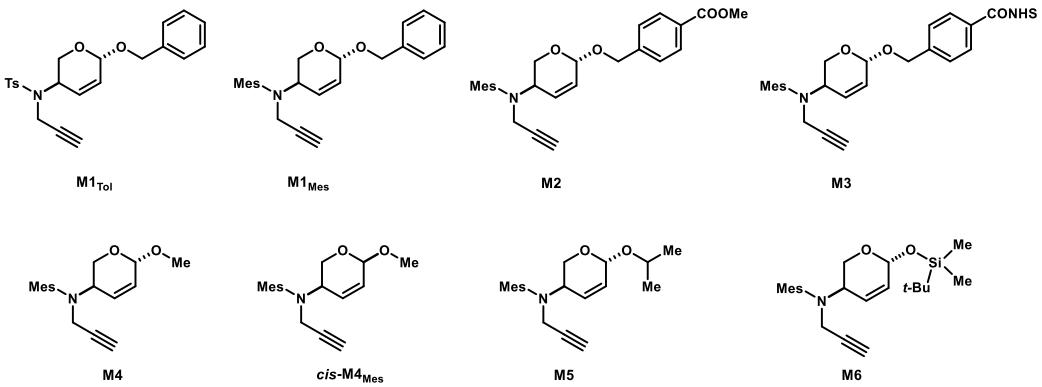

Figure 7. List of synthesized monomers.

Overall, each monomer showed high conversions in relatively short times, except for **M6$_{Mes}$** which only reached 10% conversion in 25 minutes. Data on percent conversions, conversion times, molecular weights, and PDIs can be found in **Figure 8**.

Entry	Monomer	DP (M/I)	*t* [min]	Conv [%][a]	$M_{n,SEC}^{app}$ [kDa][a]	$Đ$[a]
1	**M1$_{Tol}$**	50	15	>95%	26.1	1.18
2	**M1$_{Tol}$**	100	30	>95%	47.1	1.27
3	**M1$_{Tol}$**	200	60	91%	79.1	1.77
4	**M1$_{Mes}$**	25	6	>95%	10.6	1.13
5	**M1$_{Mes}$**	50	6	>95%	23.5	1.12
6	**M1$_{Mes}$**	100	10	>95%	43.9	1.18
7	**M1$_{Mes}$**	200	30	>95%	83.8	1.23
8	**M1$_{Mes}$**	500	45	92%	164.7	1.88
9	**M2$_{Mes}$**	100	10	>95%	47.2	1.13
10	**M3$_{Mes}$**	100	12	>95%	34.0	1.17
11	**M4$_{Mes}$**	100	10	>95%	37.4	1.24
12	**M5$_{Mes}$**	200	30	>95%	78.7	1.22
13	**M5$_{Mes}$**	500	45	>95%	171.1	1.42
14	**M6$_{Mes}$**	100	25	10%	7.0	1.50
15	***cis*-M4$_{Mes}$**	100	20	29%	18.3	1.27

Figure 8. Polymerization data for monomers synthesized.

In conclusion, this research establishes a new method of developing degradable polymers from acetal monomers using cascade enyne metathesis polymerization. Living polymerizations of

these monomers can also be achieved for the first time by tuning the size and stereochemistry of the monomer. The potential for different small molecule substituents in the acetal position provides opportunities for different functionality of the polymers as well. One possibility is cargo release functionality, which could make this monomer useful in drug delivery systems. Additionally, investigating the use of heteroatom acetals will further broaden the applications of this polymer, allowing for increased modification of the degradation windows.

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